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Tables 2

Figures 2

Depression and pain:

Primary data and meta-analysis among 237,952 people across 47 low- and middle-income countries

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Background

Depression and pain are leading causes of global disability. However, there is a paucity of multinational population data assessing the association between depression and pain, particularly among low- and middle-income countries (LMICs) where both are common. Therefore, we investigated this association across 47 LMICs.

Methods

Community-based data on 273,952 individuals from 47 LMICs were analyzed. Multivariable logistic and linear regression analysis were performed to assess the association between ICD-10 depression/depression subtypes (over the past 12 months) and pain in the previous 30 days based on self-reported data. Country wide meta-analysis adjusting for age and sex was also conducted.

Results

The prevalence of severe pain was 8.0%, 28.2%, 20.2%, and 34.0% for no depression, subsyndromal depression, brief depressive episode, and depressive episode respectively. Logistic regression adjusted for socio-demographic variables, anxiety and chronic medical conditions (arthritis, diabetes, angina, asthma) demonstrated that compare to no depression, subsyndromal depression, brief depressive episode, and depressive episode were associated with a 2.16 (95%CI=1.83-2.55), 1.45 (95%CI=1.22-1.73), and 2.11 (95%CI=1.87-2.39) increase in odds of severe pain respectively. Similar results were obtained when a continuous pain scale was used as the outcome. Depression was significantly associated with severe pain in 44/47 countries with a pooled OR of 3.93 (95%CI=3.54-4.37).

Conclusion

Depression and severe pain are highly comorbid across LMICs, independent of anxiety and chronic medical conditions. Whether depression treatment or pain management in patients with comorbid pain and depression leads to better clinical outcome is an area for future research.

Key words: Depression, pain, depressive symptoms, comorbidity

Introduction

Depression is estimated to affect 350 million people worldwide and is a leading cause of global disability (Ferrari *et al.* 2013). A confirmed diagnosis of major depressive disorder (MDD) accounts for 8.2% of the total worldwide years lived with disability (YLDs) (Ferrari *et al.* 2013). Within the past decade, there has been an increasing emphasis on the physical health challenges of people with depression (Henningsen *et al.* 2003).

Pain is also highly prevalent (Breivik *et al.* 2006) and a leading cause of global burden and YLD (Murray *et al.* 2012). The management of pain is associated with considerable financial burden (Breivik *et al.* 2013). A previous systematic review over a decade ago demonstrated that pain and depression are highly comorbid and associated with worse outcomes compared to when each condition exists on its own (Bair *et al.* 2003). Moreover, comorbid pain and depression are related to increased costs and burden on healthcare services (Rayner *et al.* 2016). Therefore, understanding the pain and depression relationship has important health and economic consequences.

To date, most of the research investigating the pain and depression relationship has focused on the Western world. For instance, in a large representative study conducted in the United Kingdom, Nicholl et al (Nicholl *et al.* 2014) found that depression was associated with increased odds of pain. Pain is also common in low- and middle-income countries (LMICs) and is in particular related to trauma, cancer, birth complications, congenital defects, and surgical complications, all potentially leading to chronic pain if not treated or if treated inadequately (Jackson *et al.* 2015, Jackson *et al.* 2016). There is however a distinct paucity of representative population cohort studies investigating associations between depression and pain in LMICs. Such data would be valuable as

depression is highly pervasive among people in LMICs (Andreasen *et al.* 2014, Guerra *et al.* 2016, Prina *et al.* 2011). Moreover, the majority of the world's population resides in LMICs and the population in this setting is expected to increase in recent decades while chronic pain is common among people living in LMICs (Jackson *et al.* 2015). However, resources to provide integrated care for pain and depression comorbidity are limited. Thus, understanding the additional mental health burden is important for planning service developments in this context.

To date, three large-scale studies have investigated pain and depression comorbidity across multiple countries including a small number of LMICs (Demyttenaere *et al.* 2007, Gureje *et al.* 2008, Tsang *et al.* 2008). These studies found that across 18 countries (8 in LMICs), people with multisite pain (Gureje *et al.* 2008) and chronic pain (Tsang *et al.* 2008) are at increased risk of mood disorders. Moreover, chronic neck and back pain is associated with an increased odds of mood disorder (Demyttenaere *et al.* 2007). Whilst helpful and clearly advancing the field, the lack of focus specifically on LMICs does not make the results generalizable to this region (only 8 countries were considered), nor give sufficient coverage and attention to this neglected phenomenon. A number of pertinent questions also remain unanswered. First, many LMICs do not have data on the pain and depression comorbidity. Second, it remains unclear whether the relationship between pain and depression is influenced by depression subtypes (i.e. brief depressive episode, subsyndromal depression and depression). Finally, whether the association between pain and depression is similar across a wide variety of countries is unknown.

Thus, the aims of the current study were to: 1) explore the relationship between pain and subsyndromal depression subtypes across 47 LMICs; 2) investigate the factors that

might influence the pain and depression relationship; and 3) conduct a country wide meta-analysis to explore if pain and depression comorbidity is significantly increased across all 47 countries. Our *a priori* hypothesis was that we would observe a consistent association between pain and depression syndromes across all LMICs, with the presence of a depression syndrome (vs. no depressive syndrome) being associated with higher levels of pain.

Methods

The survey

Secondary data analysis of the World Health Survey (WHS) was conducted. This was a cross-sectional study undertaken in 2002-2004 in 70 countries worldwide. The data are publically and freely available to all interested researchers subject to approval through the WHO website (http://www.who.int/healthinfo/survey/en/). Data were collected using single-stage random sampling and stratified multi-stage random cluster sampling across 10 and 60 countries respectively. Full details of the WHS are available in the above-mentioned WHO website. Briefly, persons aged ≥18 years with a valid home address were eligible to participate. Each member of the household had equal probability of being selected by utilizing Kish tables. A standardized questionnaire, translated accordingly was used across all countries. Linguists were utilized to ensure that the translation was conducted to a high standard.

The individual response rate (i.e. ratio of completed interviews among selected respondents after excluding ineligible respondents from the denominator) ranged from 63% (Israel) to 99% (Philippines) (Moussavi *et al.* 2007). In order to conduct the study, ethical approval was obtained from the ethical boards at each study site. Sampling weights were generated to adjust for non-response and the population distribution reported by the United Nations Statistical Division. Informed consent was obtained from all participants.

Of the 70 countries, 69 had data which is publicly available. Of these, 10 countries (Austria, Belgium, Denmark, Germany, Greece, Guatemala, Italy, Netherlands, Slovenia, and UK) were excluded due to lack of data on sampling information. Furthermore, 10 high-income countries (Finland, France, Ireland, Israel, Luxembourg,

Norway, Portugal, Spain, Sweden, United Arab Emirates) were excluded in order to focus on LMICs. Moreover, Turkey and Morocco were also excluded due to missing information on some of the variables of interest. Thus, the final sample consisted of 47 countries which corresponded to 21 low-income and 26 middle-income countries according to the World Bank classification (http://chartsbin.com/view/2438) at the time of the survey (2003) (The full list of the included countries can be found in Figure 2). The data were nationally representative in all countries with the exception of China, Comoros, the Republic of Congo, Ivory Coast, India, and Russia.

Variables

Pain (outcome variable)

Pain was assessed in two ways. Participants were asked "Overall in the last 30 days, how much bodily aches or pains did you have?" with answer options none, mild, moderate, severe, and extreme. In line with a previous publication using the same dataset (Koyanagi & Stickley, 2015), those who answered severe or extreme were considered to have severe pain. Second, another pain measure was constructed with the use of the above-mentioned question "In the last 30 days, how much bodily discomfort did you have?" which also had the same response options. A factor analysis with polychoric correlations was used in order to obtain a factor score which was converted into a scale ranging from 0 to 100 with higher scores corresponding to higher levels of pain/discomfort. This pain score has been used in previous WHS publications (Koyanagi *et al.* 2016, Nuevo *et al.* 2013).

Depression (exposure variable)

Depressive symptoms were classified based on individual questions from the WHS

version of the World Health Organization World Mental Health Composite International Diagnostic Interview which captures the duration and persistence of depressive symptoms in the preceding 12 months (Kessler & Ustun, 2004). The same algorithm as in a previously published paper from the WHS (Ayuso-Mateos *et al.* 2010) was utilized, which includes four mutually exclusive groups based on the ICD-10 Diagnostic Criteria for Research (ICD-10-DCR) (World Health Organization 1993) where criterion B referred to symptoms of depressed mood, loss of interest, and fatigability. The algorithms used to define the four groups were the following: (a) Depressive episode group: At least two criterion B symptoms with a total of at least four depressive symptoms lasting two weeks most of the day or all of the day. (b) Brief depressive episode group: Same criteria as depressive episode but did not meet the two-week duration criterion. (c) Subsyndromal depression: At least one criterion B symptom with the total number of symptoms being three or less, lasting two weeks most of the day or all of the day. The criteria of duration of at least two weeks and presence of symptoms during most of the day had to be met. (d) No depressive disorder group: None of the above. Within the results, any depression refers to depressive episode, brief depressive episode or subsyndromal depression.

Other variables

A range of other sociodemographic information was captured including sex, age, education, and wealth. For the current paper, education was categorized as: no formal education, primary education, secondary or high school completed, or tertiary education completed. Principal component analysis based on 15-20 assets was conducted to establish country-wise wealth quintiles. Anxiety was assessed by the question "Overall in the past 30 days, how much of a problem did you have with worry or anxiety?".

Those who answered severe or extreme were considered to have anxiety, in accordance with previous publications (Koyanagi *et al.* 2016, Wong *et al.* 2013). We also considered other physical health diagnoses known to be associated with pain and depression including arthritis, asthma, and diabetes, all of which were based solely on self-reported lifetime diagnosis. For angina, in addition to a self-reported diagnosis, a symptom-based diagnosis based on the Rose questionnaire was also used (Rose, 1962).

Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The difference in sample characteristics between those with and without severe pain was tested by Chi-squared tests. We assessed the association between depression and pain in two ways. First, we conducted multivariable binary logistic regression analysis which used the dichotomous severe pain variable as the outcome. Second, multivariable linear regression analysis with the continuous pain score as the outcome was also performed. The former analysis was intended to assess specific associations with extreme levels of pain for its clinical relevance, whereas the latter was intended to capture increasing levels of pain associated with depression while using a combined measure of pain and discomfort. We conducted hierarchical analysis based on wider literature to assess how the inclusion of different control variables affected the coefficient of depression. Three models were constructed: Model 1 - adjusted for socio-demographics (sex, age, education, wealth) and country; Model 2 - adjusted for socio-demographics, anxiety, and country; and Model 3 - adjusted for socio-demographics, anxiety, chronic physical conditions (arthritis, diabetes, angina, asthma), and country. Specifically, each of the variables were chosen based on past literature due to their relationship with pain and/ or depression (Bair *et al.* 2003, Rayner *et al.* 2016). To

adjust for country, dummy variables for each country were included in the models, following the methods used in previous WHS publications (Koyanagi *et al.* 2016, Nuevo *et al.* 2012). We also conducted country wide logistic regression analysis to assess the association between depression and severe pain while adjusting for sex and age. A pooled estimate was obtained by combining the estimates for each country into a random-effect meta-analysis. This was done to evaluate the generalizability of our findings across countries. The sample weighting and the complex study design were taken into account in all analyses. Results from the logistic and linear regression models are presented as odds ratios (ORs) and regression coefficients (Bs) respectively, with 95% confidence intervals (CIs). All statistical tests were two-tailed and the level of statistical significance was set at $p<0.05$.

Results

Prevalence of depression and pain

The final sample size was 237,952 with a mean age of 38.4 years of whom 49.2% were male. The prevalence of subsyndromal depression, brief depressive episode, and depressive episode were 2.5%, 2.7%, and 6.5% respectively. The prevalence of severe pain across the entire sample was 10.7%. The mean (SD) pain scores were 23.3 (26.0), 43.0 (26.2), 41.7 (26.8), and 49.9 (26.2) for no depression, subsyndromal depression, brief depressive episode, and depressive episode respectively, while the prevalence of severe pain for these four conditions were 8.0%, 28.2%, 20.2%, and 34.0% respectively.

Regression analyses

A linear increase in the prevalence of all types of depression was observed with increasing pain scores, with the increment of depressive episode being most pronounced (**Figure 1**). The sample characteristics are illustrated in **Table 1**.

Table 1 here

Figure 1 here

Female sex, older age, lower levels of education and wealth, anxiety, arthritis, diabetes, angina, and asthma were significantly associated with higher prevalence of severe pain. The association between different types of depression and pain are illustrated in **Table 2** and **Table 3**. In the logistic regression model, compared to those with no depression, depression was associated with 2.80 (subsyndromal depression) to 4.01 (depressive episode) times higher odds for severe pain after adjustment for socio-demographics (Table 2, Model 1). When anxiety was included in the model, a moderate attenuation in the ORs were observed (Table 2, Model 2) while further adjustment for chronic conditions lead to a further albeit less pronounced attenuation in the ORs with the ORs (95%CIs) for subsyndromal depression, brief depressive episode, and depressive

episode being 2.16 (1.83-2.55), 1.45 (1.22-1.73), and 2.11 (1.87-2.39) respectively in the fully adjusted model (Table 2, Model 3). Similar declines in the coefficients of depression were observed in the linear regression model across Model 1 and 3 (Table 3). Compared to those with no depression, the B-coefficient (95%CI) for subsyndromal depression, brief depressive episode, and depressive episode were 11.15 (9.62-12.68), 9.52 (8.17-10.87), and 12.52 (11.24-13.80) respectively in the fully adjusted model (Table 3, Model 3). These coefficients can be interpreted as the mean increase in the pain score (range 0-100) for that depression category when compared to those with no depression.

Table 2 here

Table 3 here

Country wide meta-analysis of depression and pain association

Finally, the results of the country-wise association between any depression and severe pain estimated by logistic regression are illustrated in **Figure 2**. The pooled OR across 47 countries adjusted for age and sex demonstrated that depression was associated with a nearly 4 fourfold increase in odds (OR 3.93; 95%CI=3.54-4.37) of severe pain. Across the 47 countries, 44 demonstrated statistically significant increased odds of depression and pain. Particularly high odds ratios were observed in China (OR 13.94), Malaysia (OR 10.33), Mauritania (OR 7.12), Mauritius (OR 6.82), Philippines (OR 6.73) and Laos (OR 6.34).

Figure 2 here

Discussion

General findings

The current study found that pain and depression are strongly associated across 44/47 LMICs. Our results provide the first evidence on the association between depression subtypes and pain in LMICs. Anxiety and chronic conditions were influential factors in the association between pain and depression but did not fully explain or ameliorate the association. Our country wide meta-analysis demonstrates that pain is associated with an increased odds of depression across most LMICs.

Despite wide variation in socio-economic, demographical and cultural characteristics across the participating countries, and in the magnitude of country-specific associations between depression and pain, several findings were consistent across the large number of countries. Our data suggests that women exhibited a higher overall prevalence of physical pain than men in line with prior research (Mogil 2012). The precise reasons for this in our data are not clear, however previous research has that the reason for this are complex and multifactorial and include psychosocial factors, hormonal factors and genetic differences (Mogil 2012, Paller *et al.* 2009)Another cross-national consistent finding that confirms published epidemiological surveys is an increased vulnerability to physical pain with increasing age (Tsang *et al.* 2008). The present study suggests that the same clinical sensitivity to comorbid mental disorders and physical pain, in particular arthritis, diabetes, angina, and asthma may be important in the elderly population. Of interest, higher education status and higher income were associated with less pain. The reason for this relationship might be an increased awareness of health risks that might cause pain and less trauma and accidents in higher educated people while those with a better socio-economic status have a better health coverage than those who can't afford it, particularly in LMICs (Asante *et al.* 2016).

There are several hypotheses which might explain why people with depression report higher levels of severe pain. First, and as indicated in the current study, is that the heightened prevalence of somatic co-morbidity among people with depression might play a role, which has been reported in previous research (De Hert *et al.* 2011b). Pain is a primary symptom of many physical health conditions and the increased pain-depression relationship could be an underlying symptom of poorer physical health. Alternatively, suboptimal treatment for physical health condition due to inequality in access to health care, stigma and discrimination and less attention by care givers to comorbidities in people with mental illness may be other explanations (De Hert *et al.* 2011a). It is established that among people with mental illness, there are health inequalities and people are less likely to receive physical healthcare (De Hert *et al.* 2011a). Thus, the heightened relationship we observed may be related to under addressed physical comorbidity. Clearly this is an issue in LMICs where resources are sparser than in established Western society. Third, inflammatory processes have been implicated in the pathogenesis of pain in depression (Bai *et al.* 2014). Recent evidence has demonstrated that depression is also associated with considerable inflammation (Strawbridge *et al.* 2015). Moreover, there is an increasing evidence base to suggest that anti-inflammatory treatments such as statins offer favourable improvements in depressive symptomology in people with depression (Salagre *et al.* 2016). Such findings seem to support the notion that depression and pain may also be linked through inflammatory pathways. Related to the inflammatory hypothesis, sedentary behaviour is also associated with inflammation (Hamer *et al.* 2012a, Hamer *et al.* 2012b) and both pain (Stubbs *et al.* 2014) and depression are associated with sedentary behaviour (Vancampfort *et al.* 2015). Given that physical activity can improve inflammatory markers (Hamer *et al.* 2014), interventions increasing activity levels may improve pain

symptoms (Uthman *et al.* 2013) and depression (Schuch *et al.* 2016a, Schuch *et al.* 2016b) and at a population level may be a particularly viable option in LMICs. Another potential explanation is that areas of the brain linked to mood dysregulation (e.g. amygdala, insular) also project to structures involved in pain modulation (e.g. periaqueductal gray). Therefore, the neurobiological changes among people with depression could increase the risk of pain. However, clearly, future research is required to explore all of the aforementioned hypotheses.

Clinical implications

Our data demonstrates that physical pain is an important problem across the depression spectrum in LMICs. Strategies to better understand this relationship and manage it are needed. For example, pain assessment, prevention and management should be integrated in the clinical practice guidelines for people across the depression spectrum. Existing health care models may benefit from adapting to actively monitor and intervene with the depression and pain comorbidity. Health care systems in LMICs including policy makers may benefit from embracing and managing the physical health needs of people with depression in healthcare services. However, a number of considerations exist. An important environmental barrier in the care of people with depression in LMICs is the lack of integrated mental and medical services and the poorly developed community-based psychiatric services (Mugisha *et al.* 2016). In addition, LMICs have limited access to most expensive novel antidepressants, as the Norepinephrine Serotonin Reuptake Inhibitor (NSRI) drugs for example, a scenario which further increase the burden associated to depression-pain interface (Pan *et al.* 2015). This is compelling considering that a considerable number of individuals living in LMICs may “manifest” depression complaining for (medically-unexplained) somatic

pain (Fornaro *et al.* 2011) rather than verbal communication of their own emotions due to stigma issues (Fornaro *et al.* 2009). Also, pain is a risk factor for self-medication and abuse of analgesic medication, with particular concerns regarding opioid medication dependence (Webster *et al.* 2016).

We suggest that pain assessment, prevention and management has an important role in health services, particularly when one considers the heightened risk of suicidal behaviours in those with painful comorbidities (Stubbs, 2016). However, it should be acknowledged that many mental health providers do not ask about physical pain in their patients because of lack of consideration of this health care aspect, lack of time or lack of resources directly available to them (De Hert *et al.* 2011a). Therefore, first of all, there is a clear need to increase awareness of the importance of physical health needs of patients with depression among mental health providers in LMICs. Continued medical education (CMEs which is a common practice in LMICs (Mugisha *et al.* 2016)) should be used to inform health providers on the importance of assessing physical pain in people with subsyndromal depression, brief depressive episode, and depressive episode. Health providers in LMICs need to be informed that their roles extend beyond taking care of the mental or physical health of their patients and assume responsibility for both the mental and physical health of their patients. There is also the need for mental health training institutions that train medical personnel to include physical pain assessment as part of their curriculum and training programs. However, effective pain screening/monitoring is not sufficient on its own, as appropriate treatment is also mandatory. Patients should be provided self-care management strategies including advise on a healthy and active lifestyle and prioritizing the prevention of chronic pain and avoiding fragmented care (De Hert *et al.* 2011a). Concomitant pain and mental health disorders often complicate pharmacological management, but several drug

classes, including serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and anticonvulsants, have efficacy for both conditions and should be considered first-line treatment agents (Hooten, 2016).

Limitations

Current findings should be interpreted in the light of some limitations. The first limitation pertains to the assessment of pain. Although the pain assessment was based on one or two dimensions of pain, specific details regarding the duration (e.g. acute or chronic), type, and site of pain were not characterized. Thus, for example, our pain measure is likely to include pain of both acute and chronic nature. Since the WHS was conducted in many different cultural settings and was primarily aimed to assess mental health issues, it was not feasible to include a more comprehensive pain assessment. Future studies with data on the site, nature, and severity of pain may provide further understanding of the pain-depression relationship. Previous research also demonstrated that self-report measures may be more amenable to under representation compared to behavioural pain measures among people with mental health diagnoses (Stubbs *et al.* 2015, Stubbs *et al.* 2016). Second, pain was only captured over the past 30 days while depression was based on past-12 month symptomatology. Therefore, it is possible that our results may not accurately capture the pain-depression comorbidity and it could be an under or over representation of this relationship. Clearly, future research should therefore consider pain and depression which occur during a concurrent period. Third, the diagnosis of subsyndromal depression, brief depressive episode, and depressive episode was not assessed by a clinical interview. Fourth, risk for type I error may exist due to the multiple comparisons conducted. However, the association between depression subtypes and pain were highly significant ($p<0.001$) and thus, this is unlikely to have influenced our main findings. Fifth, anxiety was assessed with a single question

and the specificity and sensitivity of this question against the gold standard diagnosis of anxiety disorders is not established. Therefore, future studies should include a more complete anxiety assessment and ideally use a clinical diagnosis. Moreover, information on physical conditions was limited in the WHS. Thus, we were unable to adjust for physical conditions such as cancer which may confound the pain-depression relationship. Next, there were six countries for which data were not nationally representative. However, there were no appreciable differences in the results even after the omission of these countries from the analysis. Finally, the data are cross sectional. Therefore, the directionality of the relationships cannot be deduced from our data. Nonetheless, the strengths of the study include the large sample size and the multi-national scope, including most regions of the world, but in particular LMICs in Africa, Latin America, Asia and Eastern Europe.

In conclusion, our data demonstrates that depression (particularly those with a full depressive episode) is associated with increased pain. The results were consistent across almost all of the 47 LMICs even after adjusting for multiple confounders. Clearly efforts are needed to tackle pain and depression comorbidity in LMICs. Future research is also needed to attempt to elucidate the underlying mechanisms explaining this association, which might also offer a window of opportunity for viable treatment options in this region with sparse resources.

Conflict of interest

BS, AK, DV, MF, MS, NV, TT, AFC, have no conflict of interest to declare.

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